REMARKS

1. Claims Deemed Allowable (P. 5)

Claims 50, 51, 64, 65 and 158 have been deemed allowable if rewritten in independent form. It appears to us that claims 65 and 158 may have the same scope. If such is the case, does the examiner have a preference as to which is maintained?

2. Claim Amendments

We have amended claim 1 to

(I) avoid use of the term "comprising" in the definitions of R, and R^3;

(II) permit A to be CH_2OH;

(III) delete former provisos (1), (4) and (5);

(IV) renumber former provisos (2) and (3) as (1) and (2) respectively;

(V) add a new proviso (3) permitting A to be CH_2OH; and

(VI) specify the choices for spacers and linkers.

With regard to points (II) and (V) above, claim 1 did not previously cover compounds of Formula F-A in which A was CH_2OH. However, such compounds were covered by the overlapping claim 52. In claim 52, -O- correspond to claim 1's Ch, and $-CH(-R^1)OR^4$ to claim 1's A. If in claim 52, formula F-4B, R^1=H and R^4=H, then its equivalent of claims 1's A is $-CH_2OH$.

With regard to point (VI) above, note that old claim 1 contained a definition of the linker, which has simply been

moved to the end of claim 1,[1] and that the definition of the spacer is taken from P65, L9-12.

We have cancelled claims 43-49.

Claim 50 which was deemed allowable, has been rewritten in independent form. We have therefore copied into claim 50 the definition of R3 from base claim 49.

We have cancelled claims 52-62.

Claim 63 has been rewritten in independent form and the extraneous "38" deleted (and the missing period added).

We have cancelled the withdrawn claims 66-91.

New claims have been introduced to serve as fallback positions in the event the examiner is not persuaded to withdraw the enablement rejection against the present main claim (1). Hence, it is convenient to address the basis for the new claims in the section on enablement issues.

3. Prior Art Issues

Claims 1-10 stand rejected as anticipated by Behar, "US2002/0115424 [sic, should be 6124], pp. 19-20.

The compounds of Behar paragraph [0131] correspond in a general way to formula F-A of claim 1 with the following assignments:

R2=H

R3= $C(=O)-CH(R_1)-(CH_2)x-CH_3$

[1] The definition presently specifies not more than 12 non-hydrogen atoms. There is basis for a more stringent limitation, e.g., 10, see P23, L5-6.

(R_1 as defined by Behar[2])

X = 7 to 25

A = $CH(R_2)$ OH

(R_2 as defined by Behar[3])

Ch = O

R = organic moiety comprising a carbohydrate moiety.

Our claim 1 required that at least one of five provisos be satisfied:

(1) said compound comprises at least one steroid moiety, and/or at least one alkaloid moiety;

(2) R3' comprises at least one polyunsaturated moiety;

(3) R3' is of the form -(linker)(-spacer-$T^a)_a(-T^b)_b$, where linker is an aliphatic moiety with not more than 12 non-hydrogen atoms, and consisting of one or more alkyl moieties and/or one or more spacers, a and b are integers each in the range of 0-3, and a+b is in the range of 1-3, except that if a=0, b is

---

[2] Behar's R_1 is defined by [0135] as H or OH.

[3] Behar's R_2 is defined by [0135-0142] as
(a) $-CH_2(CH_2)_yCH_3$;
(b) $-CH(OH)(CH_2)_yCH_3$;
(c) $-CH(OH)(CH_2)_yCH(CH_3)_2$;
(d) $-CH=CH(CH_2)_yCH_3$; and
(e) $-CH(OH)(CH_2)_yCH(CH_3)CH_2CH_3$;

with y=5-17.

at least 2, and T^a and T^b are, independently, organic moieties consisting of at least one *primarily alkyl* moiety and, optionally, one or more *spacers*, which may differ for each of the a instances of T^a and each of the b instances of T^b;

(4) A is -CH(-spacer-R4)-R1 where (A) R1 is hydrogen, and R4 is hydrogen or an organic moiety consisting of at least one primarily alkyl moiety and, optionally, one or more spacers; (B) R1 is an organic moiety consisting of at least one *primarily alkyl* moiety and, optionally, one or more *spacers*, and R4 is an organic moiety consisting of at least one primarily alkyl moiety and, optionally, one or more spacers; (C) R1 is -(spacer cluster)-(organic moiety) and R4 is hydrogen, -(organic moiety), or -(spacer)-(organic moiety), where each organic moiety is one consisting of at least one primarily alkyl moiety and, optionally, one or more spacers; and

(5) A is -(spacer cluster)-R1, where R1 is hydrogen or an organic moiety consisting of at least one primarily alkyl moiety and, optionally, one or more spacers.

Behar clearly did not satisfy old provisos (1) or (2) (note that Behar choice (d) for R_2 has only one C=C, and his other choices are fully saturated). Hence, we are surprised that the rejection was applied to claims 7 and 8, especially since it was not applied to claims 9 or 10. Note that the definition of "alkaloid moiety" on p. 71 requires "one or more heterocyclic nitrogen atoms". Also, old proviso (5) was not satisfied because Behar's -CH(OH)- does not qualify as a spacer (see definition at P65) and hence as part of a spacer

cluster.

Behar did satisfy provisos (3) and (4)(B) and of course only one of these provisos needed be satisfied for there to be anticipation[4].

We have deleted paragraphs (1), (4) and (5)[5]. Note that as a result of their deletion, (2) and (3) are renumbered as (1) and (2) respectively.

We have amended old proviso (3) (now numbered (2)) so that it requires that the linker be trivalent (a + b = 2) or tetravalent (a + b = 3), see discussion at P16, L24-27 and P17, L18-20. Behar's equivalent to R3' is Behar's R_1 with the proximal -C(=O)- omitted, thus

$-CH(R_1)-(CH_2)x-CH_3$ with Behar R1 = -H or -OH.

The -OH is not of course a "primarily alkyl" moiety and thus even if his -CH< is equated with our linker, he has just a=0 and b=1, with $-(CH_2)_x-CH_3$ as T_b.

In the compounds of applicants' Fig. 11, R is a carbohydrate moiety, R2 is H, and Ch=O. Hence, the

---

[4] It appears that Behar satisfies proviso (3) if our R3 is -C(Ch)-R3', R' is H, and a simple alkyl group is attached to the carbonyl carbon. It also appears that Behar satisfies proviso (4)(B), with our R1 being Behar's R2(a) (which is an alkyl), and -spacer-R4 being Behar's -OH.

[5] The deletion of (1) and (5) was not prompted by the prior art rejection but rather to reduce the enablement issues, without prejudice and disclaimer. Such is also true of the deletion of 4(A) and (C).

differences between those compounds and Behar[6] are at R3 and A:

	Claim 1 Substituents	
Compared Compounds	R3	A
Applicant's Compounds		
1 BC1-050 2 BC1-038 3 BC1-040 4 BF-1548-03 5 BF-1548-04 6 BC1-041 7 BC1-049	-CO-C_{25} alkyl -CO-C_{15} alkyl -$COCH_2$(-O-alkyl)-alkyl -polyunsaturated -polyunsaturated -CO-C_{25} alkyl -CO-C_{25} alkyl	-CH_2OH -CH_2OH -CH_2OH -CH_2OH -CHOH-CH=CH (C_{13} alkyl) -CHOH-CH=CH (C_{13} alkyl) -CHOH-C_{15} alkyl
Behar's Closest Compounds[7]		
(a)	-CO-C_{9-27} alkyl	CHOH-C_{7-19} alkyl
(d)	-CO-C_{9-27} alkyl	CH=CH-C_{6-18} alkyl

4. Definiteness (OA P. 5)

4.1. The Examiner objects to "comprises" and (all occurrences) "moiety comprising a steroidal moiety" on the grounds that it leaves the moieties open-ended.

Case law does not require that claims to chemical compounds be closed-ended. For example, in In re Barr, 444

---

[6] It can be seen that new proviso (1) covers our compounds **4** and **5**, new proviso (2) covers compound **3**, and new proviso (3) covers compounds **1-4**. Compounds **6** and **7** are not covered.

[7] For this table we set Behar's R1 to H, and Behar's R2 to (a) or (d), because those compounds are the ones most similar to applicant's.

F.2d 588, 170 USPQ 330 (CCPA 1971), the claimed compound comprised "an organic radical incapable of forming a dye with said oxidized developing agent". While the PTO's complaint was that this limitation was "negative and functional", it clearly was also open-ended.

Moreover, in the broader context of patent law, it is common to present open-ended claims to compositions, apparatus, etc. In Ex parte Schaefer, 174 USPQ 110 (PBOA 1970), the Board acknowledged that "comprising" implied that the claim omitted "some of the elements of the device", but declared this "makes the claim broad, but not vague, indefinite or misdescriptive".

Moreover, partially open ("consisting essentially of") claims are known, and one such was used in a claim to the Ziegler catalysts, Ziegler v. Phillips Petroleum, 177 USPQ 481 (5th Cir. 1973).

Also, open-ended numerical ranges are not automatically indefinite, see MPEP 2173.05(c)(II). The famous Hybritech patents, twice held valid, recite an affinity of "at least about 10^8 liters/mole", which is open-ended.

In general, case law says that claims are not to be construed as reading on impossibilities, see In re Skrivan, 427 F.2d 801, 806, 166 USPQ 85, 88 (CCPA 1970) (open-ended temperature range claim does not read on infinite temperature). Thus, the claim doesn't read on infinite length alkyl. We clearly contemplate lengths of up to C_{25} (see P36, L28 to P37, L2), C_{32} (P37, L6-8), C_{40} (P23, L1-4) and (for a PUM) C_{86} (P37, L13 and P38, L2-3). We disclose an upper limit on PUMs of 120 atoms other than hydrogen (P68, L29-30).

The present invention is directed to glycosoceramide

analogues. There are plenty of patents which recite "carbohydrate" or "polysaccharide", without a size limit.

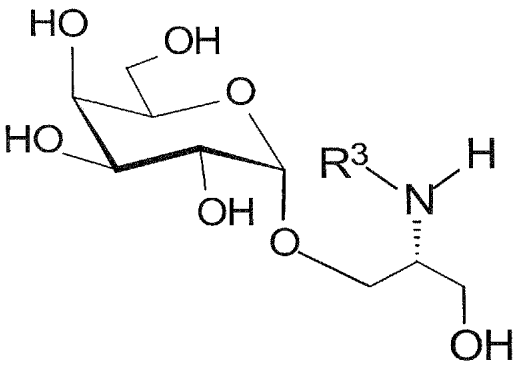
That said, we have amended claim 1 to replace the recitations that are in the form "comprising X" to instead be in the form "consisting of X and optionally including Y and/or Z". We hope that the Examiner finds this satisfactory. Note that the definition of the linker has been moved to the end of claim 1 and that the definition of the spacer is taken from P65, L9-12.

4.2. The Examiner says that claim 46 is indefinite in that F, Z and Z^1 have not been defined. First of all, there is no "F", it's "spacerF". Z is defined as "spacerF" or "spacerF-Z^1-spacerL". Z was also defined in base claim 43 in clauses (A)-(B) as a "linker moiety consisting of one or more alkyl moieties and/or one or more spacers". "SpacerF" means the first (F) spacer in Z, "spacerL" means the last (L) spacer in Z, and Z^1 is the rest of Z. Spacers are defined at P65, L8-12.

Nonetheless, claims 46 and 43 have been cancelled.

4.3. The Examiner says there is no antecedent basis for the terminology "as previously defined" in claims 63 and 74.

Claim 63 was drawn to "the compound of claim 62, <u>further defined by</u> the following structure:



wherein R3 is as previously defined.

R3, in turn, was defined by base claim 62. Hence, antecedent basis was satisfied.

We have amended claim 63 to explicitly include the enumeration of R3. Note that for consistency with a similar recitation in claim 50, the first R3 option of claim 62 is (ix) in amended 63.

Referring next to claim 74[8], this is drawn to the compound of claim 73, further defined by a structural formula, "wherein R1, R3 and X are as previously defined". R1 and R3 are defined by claim 73, so they have antecedent basis. Claim 73, in turn, is dependent on 66, which defines "X", so it, too, has antecedent basis. In any event, 74 is now cancelled.

5. Enablement (OA PP. 2-4)

Claims 1-30, 36-49, 52-63, 92-105, 107-139, 143-146 and

[8] Which was withdrawn from consideration, so we don't understand why it was rejected.

148-157 stand rejected for lack of enablement.

The examiner argues that while the "specification discloses 14[9] specific compounds having closely related structural formulas, the compound claims "encompass an immense number of species".

5.1. With regard to the compound claims, the issue is whether it requires undue experimentation to make and use the compounds claimed. The examiner nowhere suggested that it would be problematic to make the compounds of claim 1 (F-A), 36 (F-AF) 43 (F-1A) and 52 (F-4B).

The examiner clearly questions whether these compounds can be used for protection against infection or cancer. However, to enable a compound claim, it is necessary to enable just one use, and that need not be use in protection against infection or cancer. The examiner concedes that several disclosed compounds induce cytokine secretion, proliferation of splenocytes, or IFN-gamma production. The specification also discloses the possible use of the claimed compounds as mimics or inhibitors of naturally occurring glycosyslceramdies, or as immunogens (if the compound is merely haptenic, it can be conjugated to a carrier).

Since the examiner does not set forth a reason to conclude that these utilities are insufficient to support utility of a compound per se, the examiner must explain why it is unreasonable to assume that most of the compounds claimed will enjoy at least one of these activities. Merely asserting that there are an immense number of these compounds is insufficient to meet the burden of persuasion.

---

[9] We think this is including anti-CD3, cp. Figs. 11-12. And Figs. 2-10 also disclose specific structures albeit untested ones.

We respectfully submit that it is therefore appropriate to allow the claim, particularly in its present narrowed form.

In addition, due consideration should be given to the dependent claims.

5.2 *Size*

The overall size of the claimed compound is limited by old claims 2 (each of the organic moieties -- i.e., R, R2, R3 and A -- consists of not more than 120 atoms other than hydrogen), 143 (molecular weight less than 10,000 daltons), 144 (less than 5,000 daltons), 145 (less than 2,500 daltons), 146 (less than 1,000 daltons).

The specification teaches that A and R3 are each preferably at least 5, at least 10, or at least 20 carbon atoms (P22, L20-23). It also teaches that R, R2, R3 and A are each preferably not more than 40, or not more than 30, carbon atoms (P23, L2-4). It also teaches that the polyunsaturated moiety (R3 may comprise such a moiety) is preferably not more than 120, not more than 90, not more than 60, not more than 40, or not more than 30 non-hydrogen atoms (P68, L29-P69,L2). And it teaches limits on the number of sugar units in R when R comprises a carbohydrate moiety. There are additional claims with length or composition limitations specific to R, R2, R3 or A.

5.3. *R Group*

Claim 1, as amended, requires that the R group "consists of at least one carbohydrate moiety and/or at least one Pet (pentaerythritol) unit, and optionally, one or more spacers, and optionally a trivalent or tetravalent

linker...."

The present invention is directed to glycosylceramide analogues. As stated at P1, L18 to P2, L1:

> As its name suggests, a glycosylceramide combines a carbohydrate moiety and a ceramide moiety. A ceramide, in turn, comprises the divalent residue of a sphingoid base (a long-chain aliphatic amino alcohol), and a monovalent fatty acyl moiety. More particularly, it is the result of acylating the amino nitrogen of the divalent residue (-O-CH2-CH(-NH-)-R') of a sphingoid base to obtain -O-CH2-CH(-NH-R")-R' (where R' is alkyl or alkenyl, and may be hydroxylated, and where R" is a fatty acyl group, -C(=O)-R^a , where R^a is substituted or unsubstituted alkyl). The galactosylceramide is thus the result of O-linking the Galactose to the residue of the ceramide, i.e.,
>
> Galactose-O-CH2-CH(-NH-R")-R'

It is evident that the claimed analogues differ from the naturally occurring glycosylceramides at least by modification or replacement of the ceramide structurre (which, in claim 1, is the -Ch-CH2-CH(-NR2R3)-A) and, optionally of the carbohydrate moiety (R). (P12, L22-28; P32, L11-14). The carbohydrate moiety may be modified or replaced, and such modification or replacement may include introduction of the Pet unit as a "sugar equivalent" (P12, L30-P13, L1).

Possible carbohydrate moieties are disclosed in some

detail at PP. 58-60, and the Pet unit at P63-65.

The activities of alpha-galactosylceramide, beta-galactosylceramide, fucosylceramide, and lactosylceramide are set forth at PP. 30-31 and at P2, L22-P3,L4. Glucosylceramides are the principal glycosphingolipids in the photosynthetic tissues of plants (P2, L4-6) and it is evident that they must have biological activity in at least plant systems.

Galactose, fucose, lactose and glucose are not the only sugars known to occur in naturally occurring glycosphingolipids (which of course are biologically active). The sugar units may also be mannose, GalNAc, GlcNac or sialic acid. (P60, L29-31). Nor are the carbohydrate moieties necessarily monosaccharides. For example, common gangliosides include the following:

GM2-1= aNeu5Ac (2-3) bDGalp (1-?) bDGalNAc (1-?) bDGalNAc (1-?) bDGlcp(1-1)Cer

GM3 = aNeu5Ac (2-3) bDGalp (1-4) bDGlcp (1-1) Cer

GM2,GM2a(?) = bDGalpNAc (1-4) [aNeu5Ac(2-3)] bDGalp(1-4) bDGlcp (1-1) Cer

GM2b(?) = aNeu5Ac (2-8) aNeu5Ac(2-3) bDGalp (1-4) bDGlcp (1-1) Cer

GM1,GM1a = bDGalp (1-3) bDGalNAc [aNeu5Ac(2-3)] bDGalp (1-4) bDGlcp (1-1) Cer

asialo-GM1,GA1 = bDGalp (1-3) bDGalpNAc (1-4) bDGalp (1-4)

bDGlcp (1-1) Cer

asialo-GM2,GA2 = bDGalpNAc (1-4) bDGalp (1-4) bDGlcp (1-1) Cer

GM1b = aNeu5Ac (2-3) bDGalp (1-3) bDGalNAc (1-4) bDGalp (1-4) bDGlcp (1-1) Cer

GD3 = aNeu5Ac (2-8) aNeu5Ac (2-3) bDGalp (1-4) bDGlcp (1-1) Cer

GD2 = bDGalpNAc (1-4) [aNeu5Ac (2-8) aNeu5Ac (2-3)] bDGalp (1-4) bDGlcp (1-1) Cer

GD1a = aNeu5Ac (2-3) bDGalp (1-3) bDGalNAc (1-4) [aNeu5Ac (2-3)] bDGalp (1-4) bDGlcp (1-1) Cer

GD1alpha = aNeu5Ac (2-3) bDGalp (1-3) bDGalNAc (1-4) [aNeu5Ac (2-6)] bDGalp (1-4) bDGlcp (1-1) Cer

GD1b = bDGalp (1-3) bDGalNAc (1-4) [aNeu5Ac (2-8) aNeu5Ac (2-3)] bDGalp (1-4) bDGlcp (1-1) Cer

GT1a = aNeu5Ac (2-8) aNeu5Ac (2-3) bDGalp (1-3) bDGalNAc (1-4) [aNeu5Ac (2-3)] bDGalp (1-4) bDGlcp (1-1) Cer

GT1,GT1b = aNeu5Ac (2-3) bDGalp (1-3) bDGalNAc (1-4) [aNeu5Ac (2-8) aNeu5Ac (2-3)] bDGalp (1-4)bDGlcp (1-1) Cer

OAc-GT1b = aNeu5Ac(2-3) bDGalp (1-3) bDGalNAc (1-4) aXNeu5Ac9Ac (2-8) aNeu5Ac (2-3)] bDGalp (1-4) bDGlcp (1-1)

Cer

GT1c = bDGalp (1-3) bDGalNAc (1-4) [aNeu5Ac (2-8) aNeu5Ac (2-8) aNeu5Ac (2-3)] bDGalp (1-4) bDGlcp (1-1) Cer

GT3 = aNeu5Ac (2-8) aNeu5Ac (2-8) aNeu5Ac (2-3) bDGal (1-4) bDGlc (1-1) Cer

GQ1b = aNeu5Ac (2-8) aNeu5Ac (2-3) bDGalp (1-3) bDGalNAc (1-4) [aNeu5Ac (2-8) aNeu5Ac (2-3)] bDGalp (1-4) bDGlcp (1-1) Cer

GGal = aNeu5Ac (2-3) bDGalp (1-1) Cer

where
aNeu5Ac = 5-acetyl-alpha-neuraminic acid
aNeu5Ac9Ac = 5,9-diacetyl-alpha-neuraminic acid
bDGalp = beta-D-galactopyranose
bDGalpNAc = N-acetyl-beta-D-galactopyranose
bDGlcp = beta-D-glucopyranose
Cer = ceramide (general N-acylated sphingoid)

It is disclosed that at least some of the claimed glycosylceramide analogues are useful as "mimics or inhibitors of the known glycosylceramides" (P30, L26-28).

We respectfully submit that having demonstrated that galactosylceramide analogues have utility, that we have made out a prima facie case for acceptance of enablement not only for our galactosylceramide analogues, but also at least for their counterparts in which the carbohydrate moiety is one found in a naturally occurring glycosylceramide.

Moreover, applicants assert that since it is known that the carbohydrate moiety of a glycosylceramide can act as an epitope (i.e., the glycosylceramide is an immunogen or at least an antigen), see P31 L4-6, it follows that artificial immunogens or antigens may be constructed by combining other known carbohydrate epitopes with the presently disclosed and claimed ceramide analogue moieties. Numerous carbohydrate epitopes are disclosed at PP. 92-101, and these include epitopes associated with gangliosides and globosides per PP. 99-101.

This prima facie case cannot fairly be rebutted by the bare assertion that the definition of the carbohydrate moiety is too broad; the PTO must present evidence that the person of ordinary skill in the art could not select carbohydrate moieties consistent with the simple requirement of having some biological activity.

As for the use of pentaerythritol (Pet) units as replacements for sugars, the examiner's attention is respectfully directed to PP. 9-11 of the specification. Lipid A analogues are known in which a sugar unit is replaced by a Pet unit, see PCT/US03/14633, filed May 9, 2003, and incorporated by reference at P20, L28-P21, L2.

We will discuss the basis for spacers and linkers separately.

Should the examiner not be persuaded that the specification is enabling for the present scope of R in claim 1, consideration must be given to the dependent claims limiting R. R is required to <u>comprise</u> a carbohydrate moiety by new claim 159 (and old 148), to <u>be</u> a carbohydrate moiety by new 160, and to be particular carbohydrate moieties by

old claims 50, 51, 63, 65, 92 (monosaccharide), 93 (at least one hexosyl, pentosyl or nonosyl), 94 (all hexosyl, pentosyl and/or nonosyl), 95 (all Gal, Glu, Man, Fuc; their deoxy or N-acetyl derivatives, or a sialic acid), 96 (inner sugar is galactose), 97 (inner sugar is alpha galactose), and new claims 149 (R=galactose; cp. claim 50; discussed in next section), 161 (R=1-20 sugar units), 162 (R=1-6 sugar units), 163 (like 162, but dependent on 149), 163 (R is the carbohydrate moiety of a naturally occurring glycosphingolipid or glycosylceramide, or the carbohydrate epitope of a naturally occurring antigen), 164 (R is the carbohydrate moiety of a naturally occurring glycosylceramide), 165 (dep 95; the inner sugar unit is galactose or glucose, see P60, L31-32); 166 (dep. 165; the carbohydrate moiety consists of 1-6 sugar units); 167 (dep. 165; the carbohydrate moiety consists of 1-5 sugar units); 168 (dep. 167; R is the carbohydrate moiety of a naturally occurring glycosylceramide).

Basis for there being 1 sugar unit is found in original claim 92. Basis for 2-20 sugar units resides in the definition of oligosaccharide as being 2-20 sugar units (P92, L27-30). These are alternatives, so that yields the 1-20 of claim 161. 1-6 sugar units are disclosed at P58, L13-14. There is also support for 1-10 at P93, L1, 1-9 at PP92-101, 1-5 at P61, L2-3.

5.2 *Ceramide Modification and Replacement*

In the natural glycosylceramides, the ceramide as previously stated has the structure -O-CH2-CH(-NH-R")-R' (where R' is alkyl or alkenyl, and may be hydroxylated, and where R" is a fatty acyl group, $-C(=O)-R^a$, where R^a is

substituted or unsubstituted alkyl).

It is evident from comparison of the formula of claim 1 to the above definition of a natural ceramide that the following correspondences exist:

Natural Ceramide	Claimed Analogue
-O-	-Ch-
H on N	R2
R" on N	R3
R' on CH	A

5.3 *Chalcogen (Ch) Group*

It is well known in the art, and is specifically noted in the specification at P83, L15-25, that -O- and -S- are "classical isosteres". It would therefore be expected that -S- could be substituted for -O- in the compounds of Fig. 11.

Nonetheless, claim 3 specifies that "each chalcogen is oxygen". This affects not only the Ch group that connects R to the rest of the molecule, but also the choice of spacers, effectively excluding -C(=S)- and -S-.

Claim 148 combines the requirement that R be a carbohydrate moiety with the requirement that Ch be oxygen. 149 then further requires that R be galactose.

5.4. *R2 Group*

As previously noted, the R2 of our formula corresponds to a hydrogen in natural glycosylceramides.

R2 is now defined as "hydrogen, or an organic moiety

consisting of at least one primarily alkyl moiety and, optionally, one or more spacers." The term "primarily alkyl moiety" is defined at PP. 66-67, and "spacers" are now defined explicitly within claim 1.

Old claim 3 requires that R2 be hydrogen. Old claim 153 has been made dependent on 3 so that it requires that Ch be oxygen and R2 be hydrogen.

New claim 169 adds to the requirements of claim 167 that Ch be oxygen and R2 be hydrogen. 170 does the same relative to 168. New claim 171 requires that R be galactose, Ch be oxygen, and R2 be hydrogen.

5.5. *R3 Group*

The R3 group of claim 1 corresponds to the R" (fatty acyl group) in the natural glycosylceramides. The specification teaches at P2, L18-21:

> Among the naturally occurring ceramides, there is also variation in the length of the fatty acid moiety (usually 16-26, with some preference for even numbers), and in whether or not the fatty acid moiety is hydroxylated.

The effect of fatty acid chain length on activity in a series of prior art glycosylceramide analogues was discussed at P32, L24-28; P33, L14-21; P34, L5-10. The presence or absence of hydroxylation did not appear to affect activity, P33, L15-19.

Claim 1 requires that R3 "is -CH2-R3' or -C(=Ch)-R3',

where R3' is an organic moiety consisting of a polyunsaturated moiety or a primarily alkyl moiety, and, optionally, one or more spacers, and optionally a trivalent or tetravalent linker,...."

In addition, R3 is potentially constrained by provisos (1) and (2); at least one of conditions (1)-(3) must be satisfied.

Condition (1) says that R3' consists of at least one polyunsaturated moiety (PUM) and optionally one or more spacers. The polyunsaturated moiety is defined and discussed at PP68-71. Note that it must comprise at least two alkenyl (-C=C-) bonds, P68, L 15-16, and preferably there are 2-10 such bonds. Naturally occurring lipids usually have not more than six double bonds, P69, L14-16.

The PUM is preferably of the form -CH2-Rem or -spacer-Rem, wherein Rem is the remainder of the PUM, and that the preferred spacer is -C(=O)-. P68, L20-22.

The PUM may comprise a methylene-interrupted structure, which is -C=C-C-C=C-. P69, L3-11. A shorthand nomenclature for PUMs in which all alkenic bonds are in such structures is to refer to (n-x), wherein n is the carbon chain length and x is the number of carbon atoms counting from the last carbon of the terminal double bond to the final carbon of the chain. Examples of (n-6), (n-3), (n-9), (n-4), (n-1) and (n-7) PUMs occur in nature. See P69, L21-P70,L10.

There is basis for a limitation on the number of non-hydrogen atoms in the PUM (P68, L29-P69, L2).

In Fig. 11, R3 is a PUM in compounds 4 and 5. More specifically, it is of the type in which R3 is -C(=O)-R3', wherein R3' is itself a PUM. Still more particularly, it is of the type in which there are four olefinic bonds, and all

four are part of methylene-interrupted structures, and the overall arrangement belongs to the (n-6) type.

The old claims relating to R3 comprising a PUM are

7(1) Condition (1) applies.

11(7)(amended): the PUM comprises at least one methylene-interrupted pair of alkenic double bonds (-C=C-C=C-).

12(11): same carbon skeleton as arachidonic acid, i.e. 20:4 (n-6), as in first structure of Fig. 5, see P. 70, L 18-22.

154 (1)(amended): R3 is -C(=O)R3', wherein R3' is a PUM.

155 (154) R3' comprises at least two methylene-interrupted double bonds.

156 (155), R3' is (n-6) methylene-interrupted PUM.

157 (156) R3' completely specified.

The first series of new PUM-specific claims are dependent on 169, and thus constrain R to particular carbohydrate moieties, Ch to O, and R2 to hydrogen: 172 (dep. 169; R3 is -C(=O)-R3', and R3' is a polyunsaturated moiety that is a hydrocarbon), 173 (dep. 172; R3 is characterized by 10-40 carbon atoms[10] and R3' is characterized by 2-10 olefinic bonds), 174 (dep. 173; all olefinic double bonds of R3' belong to methylene-interrupted pairs of olefinic double bonds), 175 (dep. 174; R3' comprises -CH=CH-CH2-CH-CH)$_4$-).

---

[10] This combines the teachings that R3 be at least 10 carbon atoms (P22, L20-23) and that R3 be not more than 40 carbon atoms (P23, L2-4).

The second series of new PUM-specific claims are 183-186, which parallel 172-175 but are dependent on 171, and thus further require that R be Galactose.

Claims 176-182 are dependent on 169, and based on the definition of R3 in original claims 49, 62, 64, 73, and 82, and on the compounds of Fig. 11. These claims cover polyunsaturated moieties, but (save for 177 and 178) are not specific to them.

Condition(2) says that " R3' is of the form -(trivalent or tetravalent linker)(-spacer-T^a)$_a$(-T^b)$_b$, where a and b are integers each in the range of 0-3, and a+b is in the range of 2-3, and T^a and T^b are, independently, organic moieties consisting of at least one *primarily alkyl* moiety and, optionally, one or more *spacers*, which may differ for each of the a instances of T^a and each of the b instances of T^b".

Claim 1 now specifies "each trivalent or tetravalent linker being, independently, an aliphatic moiety with not more than 12 non-hydrogen atoms, and consisting of one or more alkyl moieties and/or one or more spacers".

As to the spacers, it specifies, "each spacer being selected independently from the group consisting of -NR*-, -C(=O)-, -C(=S)-, -O- and -S-, wherein R* is H or alkanyl of 1-4 carbons".

In Fig. 11, compound 3, we see an example of a trivalent linker, -C(=O)-CH2-CH<. To the "CH<" we have connected both an -O-alkanyl, and an -alkanyl, so a=1 and b=1.

If condition (3) applies (A is -CH2OH), then R3 may but need not also satisfy conditions (1) and/or (2). Thus, in Fig. 11 compounds 1 and 2, there is no trivalent or tetravalent linker within R3, but rather R3 has the

structure -(spacer)-alkanyl, in which the spacer is -O-.

The old claims relevant to R3 comprising a trivalent or tetravalent linker are

10(1): condition (2) applies (comprises trivalent or tetravalent) linker.

14(10): T^a=T^b= primarily alkyl.

17(14): linker is trivalent.

18(17): linker is $-CH_2-CH<$.

19(17)(amended): eight different R3' structures.

20 (19): limits the spacers of claim 19.

New claims 176 and 179-182 also relate to such R3s (note that these claims **also** cover polyunsaturated moieties).

Because of their dependency directly or indirectly on 169 or 171, all of the new R3 claims also impose substantial limitations on R and require that Ch be oxygen and R2 be hydrogen.

5.6. *Spacer Claim*

Claim 218 requires that the spacers be -C(=O)- or -O-.

5.7. *A-limiting Claims*

The A-group of claim 1 modifies or replaces the R' group in the ceramide moiety, as previously defined, of the naturally occurring glycosylceramides. This R' group is derived, as previously noted, from the "sphingoid base", and we teach at P2, L8-17:

> The naturally occurring sphingoid bases vary in terms of the length of the main carbon chain (usually 14-22 carbons), the number of double

bonds (usually 0, 1, or 2; the double bonds may be cis or trans, and the location(s) can vary, e.g., C-4 in sphingosine and C-8 in dehydrophytosphingosine), and the number of hydroxyl groups (usually 2 or 3; note that in a galactosylceramide, one of these hydroxyl groups becomes -OR, where R is the Gal). They can have branched chains, e.g., with methyl substituents. Much if not all of this variation is also seen among the naturally occurring glycosylceramides.

Prior art studies of glycosylceramide analogues with modified sphingoid bases are discussed at P32,L29-P33,L6; P33, L21-27; P34, L12-17.

In the series A compounds discussed beginning on page 35, the A of claim 1 corresponds to -CHOH-R1. Page 36, L4-7 teaches, "Preferably, if R1 is unsaturated, it is monounsaturated, and more preferably the unsaturated bond is a double bond between C-1 and C-2, where C-1 is the carbon nearest the N of the formula." It is thus contemplated that A can be -CHOH-alkanyl or -CHOH-alkenyl. Optional hydroxylation is taught by P36, L2-4.

In compounds **1-4** of Fig. 11, "A" is -CH2OH; in compounds **5-6**, it is -CHOH-CH=CH-alkyl; and in compound **7** it is -CHOH-alkyl.

Given that the art teaches that activity decreases as the chain length decreases, it is quite surprising to see **any** activity for compounds in which A is -CH2OH. The activity of compound **1** (BC1-050) in the assays for CD3 T-cell proliferation (Fig. 25d, 30) and IL-4 production (Fig. 25f), was admittedly very modest and inferior to other

claimed compounds. Compounds **2** (with a shorter R3) and **3** (with a branched R3) did not show activity in the assays of Figs. 25-30. Compound **4** was not able to induce T-cell proliferation (Fig. 30) but was not tested for the other activities. These compounds could still have antigenic activity, which applicants did not test for.

Compounds **5** (BF-1508-84 in Figs. 25-30; BF-1548-04 in Fig. 11)and **6** (BC1-041) both had substantial immunostimulatory activity as shown by Figs. 25-30.

The old claims limiting the A-group are as follows: 150(1): "A" comprises at least one C=C (see Fig. 11 compounds **5** and **6**), 151(1): "A": comprises at least one hydroxyl group (compounds **1-7**); 152(1): "A" is -C(OH)-C=C-$(CH_2)_{12}$-CH_3 (see Fig. 11 compounds **5** and **6**).

The following new claims, limiting A, are directly or indirectly dependent on claim 169: 187 (A is -CH2OH, -CHOH-alkanyl, -CHOH-alkenyl, -CHOH-hydroxyalkanyl or -CHOH-hydroxyalkenyl), 188 (A is -CH_2OH), 189 (A is -CHOH-alkanyl, -CHOH-alkenyl, -CHOH-hydroxyalkanyl or -CHOH-hydroxyalkenyl), 190 (said alkanyl, alkenyl, hydroxyalkanyl or hydroxyalkenyl of A does not exceed 25 carbon atoms; cp. Fig. 11 compound **1**), 190 (A is -CHOH-alkenyl or -CHOH-hydroxyalkenyl), 191 (A is characterized by a single olefinic double bond), 192 (A is -CHOH-CH=CH-alkanyl), 193 (A is CHOH-CH=CH$(CH_2)_i$ CH_3, wherein i is 6 to 20, see prior claim 49), 194 (i is 12), 195 (A is -CHOH-R1 and R1 is a substitution group as defined by prior claim 49), 196 (said alkanyl, alkenyl, hydroxyalkanyl or hydroxyalkenyl of A is characterized by 8 to 25 carbon atoms), 197 (said

hydroxyalkanyl or hydroxyalkenyl is characterized by a single hydroxyl group).

The "8" of 196 is derived from the first R1 structure in former claim 49, with i having its minmum value of 6, carbon chain length for the alkyl groups in Fig. 11 ranges from 15 to 25). The "25" is derived from the fourth R1 structure in former claim 49, with i having its maximum value of 20.

With regard to "hydroxyalkanyl" and "hydroxyalkenyl", note that P36 teaches, "Preferably, if R1 contains non-alkyl moieties, they are preferably hydroxyl moieties, more preferably not more than one such moiety." Note also the hydroxyl groups in the third and fifth R1 structures of former claim 49, and the discussion of hydroxyl groups at pp. 33-34. Thus, both hydroxylated and non-hydroxylated chains are contemplated, and monohydroxy is preferred to polyhydroxy.

New claims 198-200 parallel 187-189 but are dependent on claim 171 (R=Gal, Ch=O, R2=H). Additional A-limiting claims that are dependent on 200 are 209 (said alkanyl, alkenyl, hydroxyalkanyl or hydroxyalkenyl of A is characterized by 8 to 25 carbon atoms), 210 (hydroxyalkanyl or hydroxyalkenyl is characterized by a single hydroxyl group), 211 (A is -CHOH-alkenyl), 212 (A is characterized by a single olefinic double bond), and 213 (A is -CHOH-CH=CH-alkanyl).

5.8. *Combined R, Ch, R2, R3 and A Limitations.*

Claims 201-204 parallel 172-175 but are dependent on 189. Thus, they combine the limitations of claims 169 on R, Ch and R2, with the limitations of 172 on R3 and of 189 on

A.

Claims 205-208 parallel 172-175 but are dependent on 200. Thus, they combine the limitations of 171 on R, Ch and R2, with the limitations of 172 on R3 and of 200 on A.

Claims 214-217 parallel 172-175 but are dependent on 211. 211 further restricted 200 so A is -CHOH-alkenyl wherein the alkenyl is 8 to 25 carbon atoms.

5.9. We also respectfully direct the examiner's attention to independent claim 98, drawn to specific compounds.

5.10. With respect to method claims 107-117, we have the further issue of whether the activity set forth in Figs. 24 -30 is reasonably correlated with, and therefore predictive of, protection against viruses, microbial infection, parasites or cancer. For 118-126, it is with respect to protection against an immune disease or an inflammation. For 129-139, it is whether it is reasonable to expect stimulation of the immune system. Such stimulation could be of a non-specific (immunomodulatory) nature, perhaps by positive effect on immunostimulatory lymphokines, or of a specific nature (presentation of an epitope).

The activity tested and shown is an inhibition of in vitro proliferation of cancer cells (BALB/c splenocytes) and an effect on lymphokine production by those cells.

All of these claims are now dependent, directly or indirectly, on claim 205 (discussed in section 5.8) and we respectfully submit that the data for Fig. 11 compound **5** is sufficient to justify the claimed methods.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By:_____
Iver P. Cooper
Reg. No. 28,005

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
G:\ipc\a-c\biom\gandhila\gandhila.ptoamendment.as filed.wpd